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Research Article

Intracranial Hemorrhage Due To Vitamin K Deficiency in Infancy: Clinical and Radiological Findings

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Summary

This retrospective study presents clinical and radiological findings and outcomes of 25 infants with intracranial hemorrhage due to vitamin K deficiency and evaluates the risk factors.
Two of the infants (8%) were classical type and the others were late onset. Of the patients, 18 (72%) were male and 7 (28%) were female. Twenty four infants (96%) were being fed exclusively on breast milk. Eighteen of them (72%) had not received vitamin K prophylaxis at birth. The most disabling clinical symptoms were vomiting (44%) and convulsions (40%). The most common presentations were bulging fontanel (40%) and paleness (40%). Eleven patients (44%) showed intracranial hemorrhages at more than one site. Intraparenchymal hemorrhage was the commonest (68%) type of hemorrhage. Twelve of cases (57%) were developmentally normal. Mortality rate was 8%.
Late type is frequently associated with intracranial hemorrhage particularly intraparenchymal. Lack of administration of vitamin K at birth to breastfeed babies is the most important risk factor for intracranial hemorrhage.

Key words: Vitamin K deficiency bleeding, vitamin K-propyhylaxis, intracranial hemorrhage, infant

İnfantlarda K Vitamini Eksikliğine Bağlı İntrakraniyal Kanama: Klinik ve Radyolojik Bulgular

Özet

Bu çalışmada; K vitamini eksikliğine bağlı intrakraniyal kanaması olan 25 infantın klinik, radyolojik bulguları ve risk faktörleri geriye dönük olarak değerlendirildi.
25 olgunun 2 (%8)'si klasik tip ve 23'ü geç başlangıçlı tipte idi. 18 (%72)'i erkek ve 7 (%28)'si kız idi. Olguların 24 (%96)'ü sadece anne sütü ile beslenmekteydi. Olguların 18'ine doğumdan sonra K vitamini uygulanmıştı. En fazla görülen semptom kusma (%44) ve konvülsiyon (%40) idi. En fazla saptanan muayene bulgusu fontanel bombeliği (%40) ve solukluk (%40) idi. Onbir (%44) hastada intrakraniyal kanama birden fazla bölgede vardı ve kanama en fazla (%68) intraparankimal alana olmuştu. 12 olgu izleminde normal mental-motor gelişim gösterirken, mortalite oranı %8 bulundu.
İntrakraniyal kanama özellikle geç tipin bulgusu olup en fazla intraparankimal alanda olmaktadır. Anne sütü ile beslenen bebeklerde doğumdan sonra K vitaminin yapılmamış olması en önemli risk faktörüdür.

Anahtar Kelimeler: K vitamini eksikliğine bağlı kanama, K vitamini profilaksisi, intrakraniyal kanama, infant

INTRODUCTION

Vitamin K deficiency bleeding (VKDB) is a bleeding diathesis that occurs in otherwise healthy infants in the absence of trauma, asphyxia or infectious diseases, in the first few months of life. It may be life-threatening as an important cause of infant morbidity and mortality[3,8,11,12,13]. The clinical forms of hemorrhagic disease due to Vitamin K (VK) deficiency are classified into early (on the first day of life), classic (between the second and seventh days) and late (at 4 to 6 weeks of age) forms and idiopathic and secondary forms on the basis of age of onset and etiology respectively.

As a rare pathology, early VKDB is due almost exclusively to placental transfer of maternal drugs which inhibit VK activity in the baby[8,17]. Vitamin K is poorly transmitted across the placental barrier. These babies have very limited reserves of VK at birth, and some will soon bleed if a continuing VK intake is not supplied. Classical VKDB occurs primarily in exclusively breast fed infants who have received no or inadequate neonatal VK prophylaxis. Infants having manifestations of late hemorrhagic disease characteristically have not received VK prophylaxis at birth; have been maintained on breast milk, which has a low content of VK; and may have suffered from diarrhea or cholestatic liver disease.

Whether spontaneous or iatrogenic VKDB may occur at any site. Common sites for spontaneous bleeding are mucous membranes; skin; umbilicus; retroperitoneal region; intracranial, urinary or gastrointestinal tracts. Intracranial hemorrhage (ICH) may cause significant morbidity or mortality with a frequency of 30-60% in VKDB[17]. The serious nature of late form of VKDB is emphasized by its higher association with ICH leading to high mortality and morbidity[14-17].

Here we report the clinical and radiological findings of intracranial bleeding due to VKDB in a large series. Furthermore, the risk factors and importance of VK prophylaxis are outlined.

MATERIAL AND METHODS

In this retrospective study, hospital records of 12832 infants from 1995 to 2001 were reviewed. A total of 25 cases (0.19%) with intracranial hemorrhage due to VK deficiency were reported in this period. Hospitalization data regarding gestational age, birth weight, age of presentation, using of vitamin K prophylaxis, method of feeding, place of birth (hospital or home), maternal illness and drug use (antibiotic or anticonvulsant usage), admission symptoms, underlying illness such as gastroenteritis, physical examination findings (condition of consciousness, bulging of the anterior fontanel, bleeding of the skin, etc.;) laboratory findings including coagulation studies, complete blood count, blood smear, partial thromboplastin time (PTT), protrombin time (PT), biochemical parameters including liver function tests were recorded.

Cranial computerized tomography (CT) had been performed in all babies for the diagnosis and evaluation of ICH. The CT findings (site of hemorrhage, presence of edema, hydrocephalus or associated changes) were also recorded.

During the follow-up period (ranging from 3 months to 7 years), neurologic examination findings and the results of Denver Developmental Screening Test (21 of the infants were evaluated) were recorded.

Statistical analysis was defined as number and percentage for discrete variables and mean and standard deviation for continuous variables.

RESULTS

General characteristics of the cases presenting risk factors, PT/PTT values, localization of ICH and follow-up period and outcomes (n=25) are seen in Table 1. All infants except one were born in hospital. Of the patients, 18 (72%) were male; and male to female ratio was 2.5. Family histories of the patients were negative for any bleeding disorder. Pre and post-natal history of the babies was not remarkable and APGAR scores (first and 5th minutes) were within normal range. Only 7 of them (28%) had received prophylactic intramuscular VK administration after birth. Twenty four cases 96% were exclusively breastfed and one case was fed by breast milk and formula (Table-1). There was no known risk factor for VKDB except one patient with cholestasis had beeen diagnosed. The most disabling clinical symptoms were vomiting (44%), convulsions (40%) and warning bleeds (36%). The most common presentations were bulging fontanel (40%), paleness (40%) and loss of appetite (32%) (Table-2).

Two of our cases were diagnosed classical type VKDB and the remaining cases (92%) were late VKDB. Onset of symptoms were between 3 and 66 days (median 40 days). Eleven patients (44%) showed intracranial hemorrhages at more than one site. Intraparenchymal hemorrhage was the commonest type of hemorrhage (68%) followed by subdural (SDH) (52%); subarachnoid (SAH) (28%) and intraventricular (4%) hemorrhage (Figure 1, 2, 3) (Table-1). The location of subdural hemorrhages was most commonly tentorial (46.1%) and/or interhemisferic (30.7%); convexity (23%). No epidural and posterior fossa hemorrhage was identified. Five patients had associated organ bleedings gastrointestinal and skin.

PT and PTT values were significantly prolonged in all cases. PT values were >70” and PTT values were >120” in twenty one patients. The mean value of the PT and PTT were 26.5±8.87” (min:15.4-max:36.8”) and 42.9±9.58” (min:32.6-max:54.2”) respectively in the remaining infants (Table 1). The mean value of hemoglobin was 7.4+2.8 g/dl on admission. Thrombocyte count were in normal range in all patients. Blood biochemistry values were also normal in all cases except in one with cholestasis.

The patients were hospitalized for a mean period of 16.4±8.2 days (3-47 days). All of the cases were treated with 3 mg intramuscular VK and fresh frozen plasma. Two infants needed second doses VK. Eight infants needed endotracheal intubation and mechanical ventilation. Anticonvulsant therapy mostly phenobarbital was used in 40% of patients.

One patient was treated in colloboration with neurosurgery department in our ward. Two patients were transported to neurosurgery department for surgical treatment, one of them for drainage of hematoma (patient no: 11) and the other one for ventriculo-peritoneal shunt replacement (patient no: 18). All these 3 patients were treated with antiedematous therapy consisting of dexamethasone and mannitol because, in addition to bleeding, lethargy, anisocoria and respiratory failure signs developed in all 3 patients.

Table 1: General characteristics of the cases presenting risk factors, PT/PTT values, localization of ICH and follow-up period and outcomes (n=25).

Case no	Age of Presentation (day)	Sex	Vit K prophyl.	PT/ PTT	Bleeding localization	Follow-up Period (m)	Outcome (Denver/ neurological examination)
1	50	M	Yes	>70 >120	IPH, SDH	8 m	**Normal**
2	50	M	No	>70 >120	SDH	-	Death
3	34	M	No	>70 >120	IPH, SAH	11 m	**Normal**
4	60	M	Yes	>70 >120	IPH, SDH	10 m	**Normal**
5	33	M	No	>70 >120	SDH	12 m	**Normal**
6	24	M	Yes	>70 >120	IPH, SDH, SAH	18 m	Abnormal/ MMR
7	42	M	No	>70 >120	IPH, SDH	19 m	Abnormal/ MMR
8	66	F	No	>70 >120	SDH	24 m	**Normal**
9	32	M	No	>70 >120	IPH, SDH	19 m	Abnormal/ MMR
10	40	F	No	>70 >120	IPH, SDH	21 m	Abnormal/ hemiparesis
11	40	F	No	>70 >120	Bilateral IPH	7 y	**Normal**
12	60	M	No	>70 >120	IPH	6 m	**Normal**
13	35	M	No	>70 >120	IPH	10 m	Abnormal
14	45	M	No	>70 >120	IPH	3 m	**Normal**
15	60	M	Yes	15,4 38	IPH	36 m	Abnormal
16	40	M	Yes	>70 >120	SDH	27 m	**Normal**
17	37	F	No	>70 >120	IPH, SDH, SAH	No data	No data
18	30	M	No	28,7 47,1	IPH, SDH, SAH	-	Death
19	45	M	No	>70 >120	SDH, SAH	13 m	**Normal**
20	32	F	No	25,1 32,6	IPH	12 m	Abnormal/ CP
21	3	M	No	>70 >120	IVH	3 m	Abnormal
22	60	M	No	>70 >120	SAH	No data	No data
23	60	M	Yes	>70 >120	IPH	63 m	Abnormal
24	3	F	No	36,8 54,2	IPH	3 m	**Normal**
25	60	F	Yes	>70 >120	SAH	15 m	**Normal**

PT: Protrombin time, PTT: Partial thromboplastin time, ICH: Intracranial hemorrhage;
IPH: Intraparenchymal hemorrhage; SDH: Subdural hemorrhage; SAH: Subarachnoid hemorrhage; IVH: Intraventricular hemorrhage; MMR: Mental motor retardation; M: Male, F: Female

Table 2: Presenting signs and symptoms at the first admission of the patients (n=25)

	n	%
Vomiting	11	44
Convulsion	10	40
Warning bleeds	9	36
Bleeding at the site of injection	7	28
Bruises	2	8
Irritability	6	24
Loss of appetite	8	32
Poor sucking	6	24
Respiratory/cardiac insufficiency	4	16
Lethargy	3	12
Anisocoria	3	12

Table 3: Intracranial localizations in previously defined and in the present cases with ICH

	IPH %	SAH %	SDH %	IVH %	Cerebellar %
Aydinli et al[14] n=11	91	46	27	27	-
Pooni et al[2] n=18	68	58	53	22.2	11.1
Demirören et al[11] n=19	47.4	47.4	42.1	26.3	-
Ekelund[15] n=8	75	-	12.5	25	-
Chaou et al[16] n=32	31.3	90.6	37.5	12.5	9.4
Our study n=25	68	52	28	4	-

IPH: Intraparenchymal hemorrhage; SAH: Subarachnoid hemorrhage; SDH: Subdural hemorrhage; IVH: Intraventricular hemorrhage

One patient died of bleeding on the third day of hospitalization and the other patient that had been treated with ventriculo-peritoneal shunt was died of meningitis after six months. Mortality rate was 8%. Follow-up findings are presented in Table 1. In long term follow up 12 of cases (57.1%) were developmentally normal; while 9 of cases (42.8%) had neurologic deficits. Hydrocephalus (21%), cerebral atrophy (17.3%), encephalomalasic area (13.4 %) were the most (commonly) seen neuroradiologic findings in the follow-up period (Figure 4). The most common presenting abnormalities in the follow-up period were epilepsy (30.4%), developmental delay (21%) and hydrocephalus (21%).

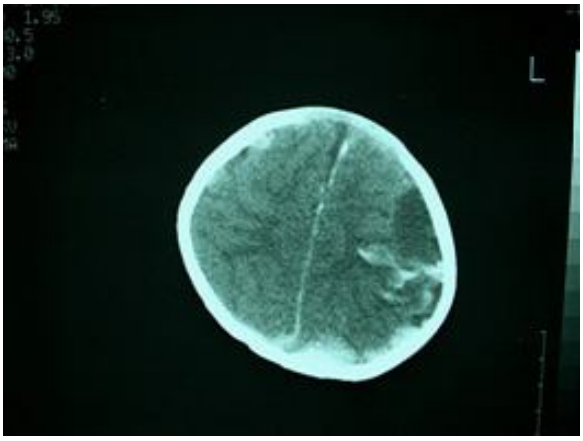

Figure 1: *Cranial CT scan of a patient with intraparenchymal, subdural and subarachnoid hemorrhage.*

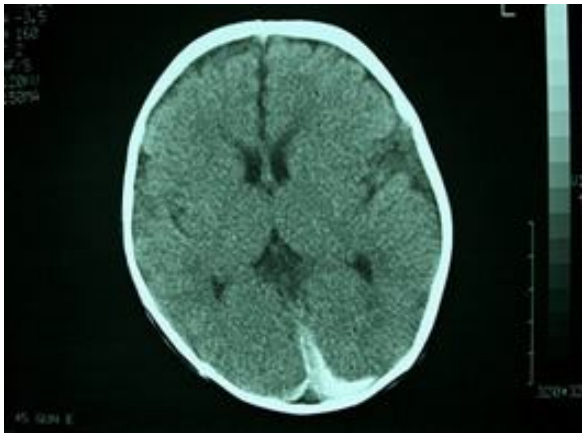

Figure 2: *Cranial CT scan of a patient with subdural hemorrhage and frontal subdural effusion.*

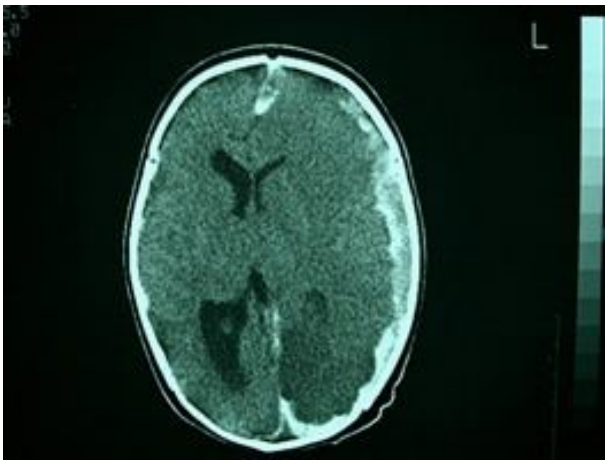

Figure 3: *Cranial CT scan of a patient with subdural and subarachnoid hemorrhage, ventricular compression, midline shift and hemispheric edema.*

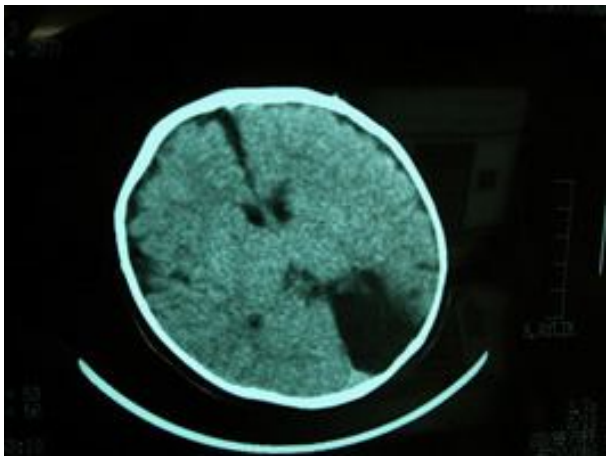

Figure 4: *Cranial CT scan of a patient in the follow-up period presenting with encephalomalasic area secondary to intraparenchymal hemorrhage.*

DISCUSSION

There are few case reports and small series available on ICH due to VKDB[2,12,15]. When dealing with an event that has a low rate of occurrence, study groups must be large enough to reflect prevalence rates accurately. The present hospital-based study was carried out to assess the relative incidence, clinical and radiological profile, risk factors and outcome of the patients with ICH due to VKDB in a relatively large series.

As mentioned before ICH may be closely associated with late type VKDB rather than the other types of VKDB[5,12,17]. In our series, we experienced also ICH in infants due to mostly late type VKDB. This rare disease was more frequent in males, all of the patients were born at term and convulsion was the most common admission symptom as seen in the literature[1,2,5]. The reason of less common in preterm infants, and also the reason of higher incidence in male infants are not clear[5,17]. The reason why VKDB is less common in preterm infants and why it shows higher incidence in male infants is not clear.

Intracranial bleeding due to VKDB may be localized in different sites and the most common localization is intraparenchymal. Pooni et al reported that the majority (79%) of the patients showed hemorrhage at more than one site[12]. In our series, eleven patients (44%) showed multiple hemorrhages, and intraparenchymal hemorrhage was the most common type (68%) followed by SAH and SDH. Consistent with Danielsson's results[4], in our study, 42.8% of the survivors had long term handicaps after ICH. Twelve of cases (57.1%) were developmentally normal and mortality rate was 8.7%. The mortality rate has been changed 0 to 46% and normal development has been reported 27% by Aydinli et al[1] and 30% by Demiroren et al[5]. Outcome after ICH is depend on the severity of the bleeding, associated intraparenchymal lesions, early diagnosis and management. Warning bleeds as the first manifestation of late VKDB may be followed by intracranial hemorrhage[1,4]. In our series, a few infants with VKDB had acute ICH; while 9 of cases had warning bleeds and 7 had bleedings at the needle-prick sites and 2 had bruises. This rather low mortality rate may be a reflection of the fact that the parents of the infants were meticulously alerted with warning bleeding signs, before the infant had ICH.

In secondary VKDB, VK metabolism can be impaired by underlying diseases such as bile duct atresia, alpha-1 antitrypsin deficiency, celiac disease, abetalipoproteinemia, cholestasis, gastroenteritis and drug use[8,10,11,12]. In our series, cholestasis in one patient was recorded as a risk factor for VKDB. In fact, this infant should have been excluded from the data because the ICH was secondary to the underlying condition.

Because breast milk contains lower amounts of VK (<5 µg/L) than cow's milk or formula (50-60 µg/L) late type VKDB occurs almost exclusively in breast-fed infants as seen in our series[5]. The prophylactic administration of VK at birth has been recommended by the Committee on Nutrition of the American Academy of Pediatrics since 1961[15]. Vitamin K prophylaxis was introduced to prevent classical type VKDB but it is still controversial as to whether or not this also protects infants against late VKDB[12]. It is suggested that VK supplementation in addition to VK prophylaxis at birth for exclusively breast-fed infants may be considered to prevent late VKDB. In our study, only 7 of our cases (28%) had received prophylactic intramuscular VK administration after birth. Although VK prophylaxis is now a routine procedure in our country, administration of VK during the neonatal period was not uniformly practiced throughout the country as well as the world during the survey period. While some clinicians suggested that VK

prophylaxis was not necessary for all full-term infants; the incidence of VKDB and associated ICH has been decreased dramatically in the countries that has been administering VK routinely[15,16]. Furthermore; administration of VK shortly after birth may be inadequate to prevent late form and VK prophylaxis may need to be repeated at the end of the first week.

In conclusion, late type VKDB is more frequently associated with intracranial hemorrhage than classical type and the most common localization of bleeding is intraparenchymal.

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REFERENCES

1. *Aydinli N, Citak A, Caliskan M, Karabocuoglu M, Baysal S, Ozmen M. Vitamin K deficiency-late onset intracranial hemorrhage. Eur J Paediatr Neurol 1998; 2:199-203.*
2. *Chaou WT, Chou ML, Eitzman DV. Intracranial hemorrhage and Vitamin K deficiency in early infancy. J Pediatr 1984; 105:880-884.*
3. *Cornelissen EAM, Kollee LAA, De Abreu RA, Motohara K, Monnes LAH. Prevention of vitamin K deficiency by weekly administration of vitamin K. Acta Paediatr 1993; 82:656-9.*
4. *Danielsson N, Hoa DP, Thang NV, Vos T, Loughnan PM. Intracranial haemorrhage due to late onset vitamin K deficiency bleeding in Hanoi province, Vietnam. Arch Dis Child Fetal Neonatal Ed 2004; 89:1546-1550.*
5. *Demiroren K, Yavuz H, Cam L. Intracranial Hemorrhage Due To Vitamin K Deficiency After The Newborn Period. Pediatric Hematology and Oncology 2004; 21:585-592.*
6. *Ekelund H. Late haemorrhagic disease in Sweden 1987-89. Acta Paediatr Scand, 1991; 80:966-8.*
7. *Hanawa Y, Maki M, Murata B, Matsuyama E, Yamamoto Y, Nagao T, et all. The second nation-wide survey in Japan of vitamin K deficiency in infancy. Eur J Pediatr, 1988; 147:472-7.*
8. *Kries RV, Shearer MJ, Göbel U. Vitamin K in infancy. Eur J Pediatr, 1988; 147:106-112.*
9. *Latini G, Quartulli L, De Mitri B, Del Vecchio A, Vecchio C. Intracranial hemorrhage associated with vitamin K deficiency in a breastfed infant after intramuscular vitamin K prophylaxis at birth. Follow-up at 18 months. Acta Paediatr 2000; 89:878-86.*
10. *Manji KP, Azzopardi D. Intracranial hemorrhage due to vitamin K deficiency following gastroenteritis in an infant. J Trop Pediatr 1999; 45:105-106.*
11. *Mc Ninch AW, Tripp JH. Hemorrhagic disease of the newborn in the British Isles: two year prospective study. BMJ 1991; 303:1105-9.*
12. *Pooni A P, Singh D, Singh H, Jain B K. Clinical profile of late hemorrhagic disease of the newborn in Punjab, India. Journal of Tropical Pediatrics 2002; 48: 312-313.*
13. *Shapiro A D, Jacobson L J, Armon M E, Johnson M J M, Hulac P, Lane P A, et all. Vitamin K deficiency in the newborn infant: Prevelance and perinatal risk factors. J Pediatr 1986; 109:675-680.*
14. *Solves P, Altes A, Ginovart G, Demestre J, Fontcuberta J. Late hemorrhagic disease of the newborn as a cause of intracerebral bleeding. Ann Hematol 1997; 75:65-66.*
15. *Soylu H, Aslan Y, Sari A, Erduran E. Intracerebral hemorrhage: A rare late manifestation of vitamin-K deficiency in a breastfed infant. The Turkish Journal of Pediatrics 1997; 39:265-269.*
16. *Sutor AH. New Aspects of Vitamin K Prophylaxis. Seminars in thrombosis and hemostasis 2003; 29(4): 37-376.*
17. *Sutor AH, Von Kries R, Cornelissen EAM, McNinch AW, Andrew M. Scientific and Standardization Committee Communications. Vitamin K Deficiency Bleeding (VKDB) in infancy. Thromb Haemost 1999; 81:456-61.*
18. *Suzuki K, Fukushima T, Megura K, et al. Inracranial hemorrhage in infant owing to vitamin K deficiency despite prophylaxis. Child's Nerv Syst 1999; 15:292-294.*